Osteoblast expression of an engineered Gs-coupled receptor dramatically increases bone mass.

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Public Summary:

Scientific Abstract:
Osteoblasts are essential for maintaining bone mass, avoiding osteoporosis, and repairing injured bone. Activation of osteoblast G protein-coupled receptors (GPCRs), such as the parathyroid hormone receptor, can increase bone mass; however, the anabolic mechanisms are poorly understood. Here we use "Rs1," an engineered GPCR with constitutive G(s) signaling, to evaluate the temporal and skeletal effects of G(s) signaling in murine osteoblasts. In vivo, Rs1 expression induces a dramatic anabolic skeletal response, with midfemur girth increasing 1,200% and femur mass increasing 380% in 9-week-old mice. Bone volume, cellularity, areal bone mineral density, osteoblast gene markers, and serum bone turnover markers were also elevated. No such phenotype developed when Rs1 was expressed after the first 4 weeks of postnatal life, indicating an exquisite temporal sensitivity of osteoblasts to Rs1 expression. This pathway may represent an important determinant of bone mass and may open future avenues for enhancing bone repair and treating metabolic bone diseases.

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